Trophoblast lineage specification, differentiation and their regulation by oxygen tension.

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Public Summary:
This manuscript reviews what is currently known about growth and development of human placental cells (trophoblast), and how these processes are regulated by oxygen tension. It is generally known that the early human placenta develops under conditions of low oxygen tension (hypoxia). However, there have been conflicting reports about how hypoxia controls trophoblast growth and differentiation. This review attempts to resolve these conflicting reports through comparison of methods used in the different reports, and also points out where gaps in knowledge remain, requiring further study.

Scientific Abstract:
Development of the early embryo takes place under low oxygen tension. Under such conditions, the embryo implants and the trophectoderm, the outer layer of blastocyst, proliferate, forming the cytotrophoblastic shell, the early placenta. The cytotrophoblasts (CTBs) are the so-called epithelial 'stem cells' of the placenta, which, depending on the signals they receive, can differentiate into either extravillous trophoblast (EVT) or syncytiotrophoblast (STB). EVTs anchor the placenta to the uterine wall and remodel maternal spiral arterioles in order to provide ample blood supply to the growing fetus. STBs arise through CTB fusion, secrete hormones necessary for pregnancy maintenance and form a barrier across which nutrient and gas exchange can take place. The bulk of EVT differentiation occurs during the first trimester, before the onset of maternal arterial blood flow into the intervillous space of the placenta, and thus under low oxygen tension. These conditions affect numerous signaling pathways, including those acting through hypoxia-inducible factor, the nutrient sensor mTOR and the endoplasmic reticulum stress-induced unfolded protein response pathway. These pathways are known to be involved in placental development and disease, and specific components have even been identified as directly involved in lineage-specific trophoblast differentiation. Nevertheless, much controversy surrounds the role of hypoxia in trophoblast differentiation, particularly with EVT. This review summarizes previous studies on this topic, with the intent of integrating these results and synthesizing conclusions that resolve some of the controversy, but then also pointing to remaining areas, which require further investigation.